DISEASE MANAGEMENT

Pharmacological options for maintenance treatment of opioid dependence include opioid agonists and antagonists

Current pharmacotherapy for the treatment of opioid dependence is based, for the most part, on stabilization of the neuropathological changes associated with this chronic condition. Opioid agonists (e.g. methadone and buprenorphine) and opioid antagonists (e.g. naltrexone) effectively reduce opioid use, promote retention in treatment and enhance relapse prevention.

Opioid dependence has a global impact

Opioid dependence is a chronic, relapsing condition that manifests as addiction to heroin and pharmaceutical opioids.[1] A worldwide increase in the misuse of opioids has been observed.[2] Globally, there are an estimated 15.6 million illicit opioid users, 11 million of whom primarily use heroin.

The global economic burden of opioid dependence is profound, both directly in terms of HIV and hepatitis C virus transmission and healthcare costs, and indirectly through criminal activity, absenteeism and lost productivity.[2] In all countries, there is a gap between the number of individuals who need treatment for opioid dependence and those receiving such treatment.

Greater understanding of the neurobiological basis of opioid dependence, the public health benefits from providing such treatments, and refinement of medications that can be delivered in general medical settings have begun to address the gap between the numbers of patients and the number of available providers.[1] This article provides an overview of the pharmacological options available for the maintenance treatment of opioid dependence, as reviewed by Tetrault and Fiellin.[1]

Definition of opioid dependence

Opioid dependence is defined by the *Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition* (DSM-IV)[3] as a maladaptive pattern of opioid use leading to clinical impairment or distress manifested within a 12-month period by three or more of the following:

- tolerance (i.e. increased amounts of opioids to achieve intoxication or the desired effect, or diminished effects with continued use of the same amount of opioid);
- withdrawal (manifested by the characteristic withdrawal syndrome, or use of opioids to relieve or avoid withdrawal symptoms);
- use of opioids in larger amounts or over a longer period of time than intended;
- persistent desire or unsuccessful attempts to cut down or control opioid use;
- great deal of time spent obtaining opioids, using opioids or recovering from their effects;
- loss of interest in social, occupational or recreational activities;
- opioid use despite knowledge of physical or psychological problems.

Drug treatment is rational ...

The neurobiological changes seen in opioid dependence lend support to the use of long-term maintenance pharmacotherapies (table I) to stabilize these complex biochemical systems.[1] Of note, although opioid detoxification strategies may be considered a component of a comprehensive treatment plan for patients with opioid dependence, these strategies *per se* have not proven effective in promoting long-term abstinence in the majority of patients. In contrast, the use of maintenance pharmacotherapy for the management of opioid dependence is associated with reduced illicit drug use, minimal euphoria, decreased adverse consequences resulting from opioid use (e.g. HIV infection, overdose), and a reduction in opioid withdrawal symptoms.

Table I. Commonly available pharmacological options for maintenance therapy for opioid dependence(1)

Medication	Action	Administration route	Usual effective dose	Frequency
Buprenorphine	Partial opioid agonist	Sublingual	8–24 mg	Daily to three times per week
Buprenorphine/naloxone	Partial opioid agonist/ opioid antagonist	Sublingual	8–24 mg/2–6 mg	Daily to three times per week
Methadone	Opioid agonist	Oral	20–100 mg	Daily
Naltrexone	Opioid antagonist	Oral	50–100 mg	Daily

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Although pharmacotherapies for opioid dependence are often applied in conjunction with psychosocial counselling, the beneficial effects of such counselling remains controversial.[1]

… from a neurobiological perspective

As with many addictive substances, opioid exposure affects dopaminergic pathways in the ventral tegmental area and nucleus accumbens of the mesolimbic forebrain.[1] Chronic opioid exposure causes changes in G protein-coupled receptors, second messenger synthetic enzymes and protein kinases that mediate the reinforcing action of opioids. Chronic exposure additionally produces neurochemical and structural neuronal changes that may persist long after the opioid pressure is removed. These changes result in a hypersensitization of the brain's reward system such that the individual may experience pathological wanting (i.e. craving) independent of the occurrence of withdrawal symptoms, which leads to a state of compulsive drug-seeking and drug-taking behaviour. The increased understanding of the neurobiological basis of opioid dependence has resulted in the emergence of the chronic disease model of opioid dependence, which includes the need for long-term pharmacological maintenance treatment and counselling.[1]

Methadone is beneficial …

Methadone hydrochloride (table I), a synthetic opioid agonist at the μ-opioid receptor, shows rapid, high-affinity binding that persists for up to 48 hours after oral administration.[1] At therapeutic dosages, methadone effectively suppresses opioid craving, blocks the euphoric effects of exogenous opioids (i.e. 'narcotic blockade') and stabilizes psychosocial functioning. Furthermore, methadone treatment has been associated with decreases in criminal behaviour, HIV risk behaviour and HIV seroconversion among injection drug users.

In clinical practice, the dose of methadone for each individual is up-titrated from a low dose to a stable maintenance dose.[1] Careful attention should be paid to the comfort of the patient and the establishment of narcotic blockade. In most cases, the patient is maintained on this dose without further need for dose titration once narcotic blockade has been achieved. The availability of methadone as a treatment for opioid dependence varies widely between countries; for instance, in the US, its use is restricted to federally regulated opioid treatment facilities, whereas Australia and some EU countries allow the prescription of methadone in general medical settings with dispensing performed at pharmacies.[1]

… but is not without risks

Common adverse events associated with methadone maintenance treatment include constipation, excessive sweating, drowsiness and decreased libido.[1] Recent studies have also suggested that methadone treatment may be associated with male secondary hypogonadism, and decreased vitamin D levels and bone mineral density.[4,5] One serious potential adverse event with higher doses of methadone treatment is a risk of QT interval prolongation.[6-8]

As a potent full opioid agonist, there is also a risk of overdose among opioid-naive individuals if medication is diverted from its intended use.[1] In addition, due to its unique pharmacokinetics with a prolonged half-life and duration of action, the majority of addiction treatment-related methadone overdoses occur within the first 30 days of therapy due to dose escalations being too rapid.

Drug interactions also require careful consideration when prescribing methadone therapy, since methadone is primarily metabolized by the hepatic cytochrome P450 (CYP) 3A4.[1] Table II summarizes the more common potential pharmacokinetic drug interactions. Pharmacodynamic drug

Table II. Some common pharmacokinetic drug interactions associated with methadone(1,9)

Coadministered drug	Pharmacokinetic effect	Treatment action
Inducers of CYP enzymes (e.g. rifampicin, phenytoin, carbamazepine, phenobarbitone, St John's wort)	↑ Metabolism of methadone	May need to ↑ methadone dose
Inhibitors of CYP enzymes (e.g. cimetidine, fluvoxamine, ciprofloxacin, fluconazole)	↓ Metabolism of methadone	May need to ↓ methadone dose
Zidovudine	Possible ↑ metabolism of methadone Possible ↓ metabolism of zidovudine	May need to ↑ methadone dose and/or ↓ zidovudine dose
Antiretroviral drugs (e.g. efavirenz, darunavir, nevirapine)	↓ Concentrations of methadone	May need to ↑ methadone dose
Desipramine	Possible ↓ metabolism of desipramine	May need to ↓ desipramine dose

CYP = cytochrome P450; ↑ indicates increase(d); ↓ indicates decrease(d).

interactions associated with methadone include additive effects when taken with alcohol, other opioids or other CNS depressants. Extreme caution is necessary when methadone is used concomitantly with other agents that are known to have the potential to prolong the QT interval, and caution is advised when methadone is used concomitantly with agents that are capable of inducing electrolyte disturbances.[9]

Other options include buprenorphine alone or with naloxone …

Buprenorphine (table I), a high-affinity partial agonist at the μ-opioid receptor and an antagonist at the κ-opioid receptor, is a well established and effective alternative to methadone for the management of opioid dependence.[1] It has an advantage over methadone in that it is a partial agonist at the μ-opioid receptor and thus, there is a ceiling effect for common agonist effects, such as analgesia and respiratory depression. If it is given in the presence of opioids or opioid metabolites, especially in opioid-dependent individuals, precipitated withdrawal will occur.

Injection misuse of buprenorphine has created concerns in certain countries, leading to the introduction of a fixed-dose buprenorphine/naloxone tablet (table I). Naloxone, a high-affinity μ-opioid receptor antagonist, is not appreciably absorbed when administered via the sublingual route. It is added to formulations of sublingual buprenorphine to deter the misuse or diversion of this medication through the injection route. However, this formulation may still be misused via the intravenous route in opioid-naive individuals or those receiving buprenorphine maintenance.[1]

Adverse effects most frequently associated with buprenorphine or buprenorphine/naloxone include headache, and the common opioid-related adverse effects of constipation, sweating and decreased libido.[1] Many of these abate with continued exposure to the medication or with dose titration. As a thebaine derivative, one potential adverse effect of note is elevated liver transaminase levels, which is of particular concern in patients with chronic hepatitis C infection.[1]

Buprenorphine and buprenorphine/naloxone are also associated with drug interactions. Like methadone, buprenorphine is metabolized by the CYP3A4 system.[1] Respiratory depression and overdose were reported in six patients abusing benzodiazepines during buprenorphine therapy.[10] Potential interactions with atazanavir and other antiretroviral medications are plausible; however, they do not appear to be clinically significant.[1]

… but not levomethadyl

Levomethadyl acetate hydrochloride, a long-acting opioid agonist, has been withdrawn from EU and US markets over concerns of cardiac QT prolongation and torsades de pointes.[11]

Oral naltrexone has a limited role …

Opioid antagonists, such as naltrexone, block the euphoric effects of opioids, diminishing the reinforcing effects of heroin and pharmaceutical opioids, and potentially extinguishing the association between conditioned stimuli and opioid use.[2] Opioid antagonists have no addictive potential and do not induce tolerance. Naltrexone (table I), a derivative of naloxone, has a 20-fold higher affinity for the μ-opioid receptor than morphine.

However, despite its rapid absorption after oral administration and prolonged duration of effect (≤72 hours), the use of naltrexone for the treatment of opioid dependence has been limited.[1] Initiating therapy may be difficult in many individuals due to the requirement of attaining prolonged (e.g. 7 days) abstinence and because of complications that may arise during this initiation period (i.e. precipitated withdrawal, relapse and early dropout). Indeed, a meta-analysis concluded that oral naltrexone, with or without psychotherapy, was no better than placebo or no pharmacotherapy in terms of retention in treatment, use of the primary substance of abuse or side effects.[12]

Potential adverse effects of naltrexone include epigastric pain, nausea, headache, dizziness, nervousness, fatigue and insomnia.[1] At higher dosages (up to 300 mg/day) naltrexone may be hepatotoxic, although hepatic safety at recommended doses has been shown in a cohort of patients co-infected with HIV and hepatitis C.[13]

Although naltrexone is metabolized by CYP3A4, this is not its primary route of metabolism.[1] Naltrexone also does not appear to be an inducer or inhibitor of CYP3A4 and, therefore, appears unlikely to be associated with drug interactions with medications that are inducers or inhibitors of this enzyme. Concomitant use of opioid agonists or yohimbine is contraindicated in patients receiving naltrexone.[1]

… but sustained-release formulations may have benefits

Sustained-release implants and depot injection formulations of naltrexone may help address the issue of adherence to naltrexone.[1] Clinical studies have shown that sustained-release formulations of naltrexone are more effective than placebo in terms of reduced opioid use and craving, and improved treatment retention. An extended-release, once-monthly intramuscular injection of naltrexone is approved for the treatment of opioid dependence in the US[14] and some other countries. Depot implants of naltrexone that

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release controlled amounts of the drug for up to 3 months are also available in some countries.[1]

Potential role for sustained-release buprenorphine …

Sustained-release formulations of buprenorphine have been developed, at least in part, to address concerns about adherence and diversion.[1] In a 6-month, placebo-controlled trial[15] during which all patients received ancillary drug counselling, patients receiving an implantable formulation of buprenorphine (providing 6 months of medication) had a significantly ($p = 0.04$) higher rate of opioid abstinence during the first 16 weeks of treatment than those receiving a placebo implant (mean 40% vs 28% of the urine samples). Treatment retention was also longer in the buprenorphine group. However, patients in both treatment arms required supplemental sublingual buprenorphine, suggesting that the implants provided less than adequate doses of buprenorphine.

… and diamorphine (heroin)

In a limited number of countries, diamorphine (heroin) is available to treat heroin dependence in highly supervised settings.[1] A meta-analysis[16] of diamorphine maintenance therapy in individuals with a history of failing prior outpatient treatment (generally with methadone) concluded that, based on the available evidence from eight clinical trials, there was a small added value of heroin prescription for long-term, treatment-refractory opioid users. Adverse events reported in diamorphine recipients included infections and overdose.

Is there a role for herbal remedies?

To date, a definitive role for herbal medicines, such as kratom and Chinese herbal medicines (e.g. WeiniCom), in the treatment of opioid dependence has not been established.[17] Although herbal medicines may complement existing evidence-based treatment, they require further testing in well designed clinical trials before they can expect to gain widespread acceptance in the management of opioid dependence. Limitations to their use include a lack of pharmacokinetic data, a lack of supportive data from rigorous, well controlled clinical trials, and their association with severe toxicity, the cause of which remains to be definitively established.[17]

Disclosure

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